Long-Term Trends in Cardiorespiratory Fitness and the Incidence of Type 2 Diabetes

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OBJECTIVE — Whereas single assessments of cardiorespiratory fitness have been shown to predict lower incidence of type 2 diabetes, there are no data on long-term trends in fitness and risk. We investigated the relationship between long-term trends in fitness and the incidence of type 2 diabetes.

RESEARCH DESIGN AND METHODS — A cohort of 4,187 Japanese men free of diabetes completed annual health checkups and fitness tests for estimated maximal oxygen uptake at least four times over 7 years (1979–1985). We modeled the trend in fitness over 7 years for each man using simple linear regression. Men were then divided into quartiles based on the regression coefficient (slope) from the model. During the follow-up period (1985–1999), 274 men developed diabetes. Hazard ratios (HRs) and 95% CIs for the incidence of diabetes were obtained using the Cox proportional hazards model.

RESULTS — Men in the lowest quartile of the distribution decreased in fitness over the 7 years (median slope −1.25 ml/kg/min), whereas men in the highest quartile increased in fitness (median slope 1.33 ml/kg/min). With adjustment for age, initial fitness level, BMI, systolic blood pressure, cigarette smoking, alcohol intake, and a family history of diabetes and use of the lowest quartile, the HRs (95% CI) for the second through fourth quartiles were 0.64 (0.46–0.89), 0.40 (0.27–0.58), and 0.33 (0.21–0.50), respectively ($P_{trend} < 0.001$).

CONCLUSIONS — These results indicate that the long-term trend in fitness is a strong predictor of the incidence of type 2 diabetes in Japanese men.

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Type 2 diabetes is a global problem with devastating human, social, and economic impact. Today >240 million people worldwide are living with diabetes. Each year another 7 million people develop diabetes. Thus, the prevention of type 2 diabetes is an important public health priority (1).

It is well known that physical inactivity is one of the primary causes of type 2 diabetes (2,3). Previous cohort studies also have shown a strong inverse relationship between cardiorespiratory fitness and the incidence of type 2 diabetes (4–7). However, these studies considered only once or twice measures of fitness level at baseline as the exposure. There are no data on long-term trends in activity or fitness as they relate to the risk of developing type 2 diabetes. Several randomized controlled trials of lifestyle, including physical activity, healthful diet, and weight reduction, in relation to type 2 diabetes over a period of years, have shown that such lifestyle changes decrease the incidence of developing type 2 diabetes among individuals with impaired glucose tolerance (8–10). No data are available from individuals at usual risk. This study was thus designed to investigate the relationship between long-term trends in fitness and the incidence of type 2 diabetes using a cohort study design among nondiabetic Japanese men.

RESEARCH DESIGN AND METHODS

Participants were employees of the Tokyo Gas Company that supplies natural gas to the Tokyo area. All employees received annual health checkups and completed a health questionnaire in accordance with the Industrial Safety and Health Law. Employees are required by law to participate.

The participants for this study were 5,984 male employees who had participated in an annual health checkup and annual submaximal exercise tests in 1985. Among these men, 335 were excluded because they were found at the health checkup to have at least one of the following: diabetes ($n = 102$), cardiovascular disease including hypertension ($n = 228$), tuberculosis ($n = 3$), or gastrointestinal disease ($n = 9$). For the present study, we also required participants to have at least four submaximal exercise tests in the previous 7 years (1979–1985). This excluded 1,462 men, leaving 4,187 men, who were followed until June 1999 for the development of type 2 diabetes.

Cardiorespiratory fitness test

Participants underwent a submaximal exercise test on a cycle ergometer to assess fitness. This test consisted of two to three progressively increasing 4-min exercise stages. The initial exercise loads were 600, 525, and 450 kilopond meter/min for participants aged 20–29, 30–39, and 40–49 years, respectively. Heart rate was

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Table 1—*Baseline characteristics by cardiorespiratory fitness trend*

Characteristic	All men	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* value
n	4,187	1,047	1,048	1,046	1,046	
Median regression coefficient or slope (ml/kg/min)	−0.04 (−6.41 to 6.19)	−1.25 (−6.41 to −0.77)	−0.40 (−0.77 to −0.04)	0.32 (0.04–0.73)	1.33 (0.73–6.19)	<0.001
Age (years)	32.0 ± 4.3	31.4 ± 4.0	32.2 ± 4.0	32.6 ± 4.2	32.0 ± 4.9	<0.001
Initial cardiorespiratory fitness (1979), predicted Vo_{2max} (ml/kg/min)	40.0 ± 6.9	45.3 ± 6.7	40.5 ± 5.5	38.1 ± 5.6	36.3 ± 6.3	<0.001
BMI (kg/m^2)	23.0 ± 2.5	22.9 ± 2.5	23.1 ± 2.5	23.0 ± 2.6	22.9 ± 2.5	0.237
Systolic blood pressure (mmHg)	125.5 ± 11.7	125.8 ± 11.3	125.9 ± 11.8	125.6 ± 11.9	124.5 ± 11.7	0.020
Diastolic blood pressure (mmHg)	72.9 ± 8.9	72.9 ± 8.9	72.9 ± 9.3	73.6 ± 8.8	72.2 ± 8.8	0.004
Current smokers (%)	68.1	70.1	71.3	67.5	63.5	0.003
Current drinkers (%)	71.1	71.2	71.4	73.0	69.0	0.178
Family history of diabetes (%)	23.5	21.9	25.2	25.1	21.7	0.083

Data represent median (range), mean ±SD, or %.

calculated from the R-R interval on an electrocardiogram, and 85% of the age-predicted maximal heart rate (220 − age [years]) was set as the target heart rate. The exercise load was increased by 225 kilopond meter/min for each stage among all age-groups, until heart rates during the course of the exercise reached the target heart rate or until the completion of the third stage. Maximal oxygen uptake (Vo_{2max}) was estimated using the Åstrand-Ryhming nomogram (11) and the Åstrand age correction factors (12).

First, we used a simple linear regression of Vo_{2max} against time to assess the individual regression coefficient (slope) of fitness over 7 years. Next, all participants were divided into quartiles based on the slope from their individual model. Initial fitness levels in 1979 were estimated using the regression line.

Diagnosis of type 2 diabetes

The annual health checkup included measurement of height, body weight, and blood pressure and a urinary glucose test. Fasting plasma glucose tests have been used since 1988.

During 1985–1999, participants were followed for the development of type 2 diabetes, which was based on any one of the following three diagnostic parameters: *1*) plasma glucose levels exceeded 11.1 mmol/l (200 mg/dl) 2 h after an oral glucose tolerance test, conducted in men with urinary glucose detected at a follow-up annual health checkup, *2*) participants themselves reported current therapy with hypoglycemic medication (insulin or oral hypoglycemic agent) when they were interviewed at their health checkup, or *3*) fasting plasma glucose levels were >7.0 mmol/l (126 mg/dl).

Statistical analysis

We first compared baseline characteristics of participants according to quartiles of the fitness trend using one-way ANOVA for continuous variables and a χ^2 test for categorical variables as appropriate. We used Cox proportional hazards models to estimate the hazard ratios (HRs) of the incidence of type 2 diabetes. We adjusted for age, initial fitness level (continuous Vo_{2max}), BMI (continuous variable), systolic blood pressure (continuous variable), cigarette smoking (nonsmokers, 1–20 cigarettes/day, and ≥21 cigarettes/day), alcohol intake (none, 1–45 g/day, and ≥46 g/day), and a family history of diabetes (present or not) in a

Table 2—*Adjusted HR for incidence of type 2 diabetes by potential risk factors at baseline (1985)*

Variable	Participants	HR (95% CI)	*P* value	P_{trend} value
Age (years)				
22–30	1,614 (38.5)	1.00 (referent)	—	
31–35	1,497 (35.8)	1.20 (0.89–1.62)	0.241	0.018
36–40	1,076 (25.7)	1.45 (1.06–1.99)	0.019	
Initial (1979) cardiorespiratory fitness (ml/kg/min)				
<35.0	961 (23.0)	1.00 (referent)	—	
35.0–39.9	1,213 (29.0)	0.88 (0.66–1.18)	0.386	0.003
40.0–44.9	1,083 (25.9)	0.72 (0.50–1.02)	0.065	
≥45.0	930 (22.2)	0.50 (0.31–0.81)	0.005	
BMI (kg/m^2)				
<21.0	949 (22.7)	1.00 (referent)	—	
21.0–22.9	1,299 (31.0)	1.45 (0.84–2.48)	0.180	<0.001
23.0–24.9	1,125 (26.9)	2.52 (1.51–4.20)	<0.001	
≥25.0	814 (19.4)	5.34 (3.23–8.82)	<0.001	
Systolic blood pressure (mmHg)				
<120	1,209 (25.4)	1.00 (referent)	—	
120–129	1,317 (26.2)	1.32 (0.92–1.90)	0.135	0.001
130–139	1,248 (22.7)	1.30 (0.91–1.86)	0.149	
≥140	413 (25.7)	2.17 (1.46–3.23)	<0.001	
Cigarette smoking				
None	1,336 (31.9)	1.00 (referent)	—	
1–20/day	1,609 (38.4)	1.20 (0.89–1.61)	0.224	0.151
≥21/day	1,242 (29.7)	1.25 (0.92–1.69)	0.150	
Alcohol intake				
None	1,209 (28.9)	1.00 (referent)	—	
1–45 g/day	2,731 (65.2)	1.64 (1.20–2.24)	0.002	0.008
≥46 g/day	247 (5.9)	1.59 (0.96–2.62)	0.071	
Family history of diabetes				
No	3,204 (76.5)	1.00 (referent)	—	
Yes	983 (23.5)	3.26 (2.57–4.14)	<0.001	

Data are *n* (%) unless otherwise noted. *Adjusted for all items in the table.

multivariate model. A family history of diabetes was defined as the known presence of family members with diabetes in any of three generations, as determined by self-report on the health questionnaire. The proportionality assumption of the model was tested using a log-minus-log plot; no evidence of violation was found. All analyses were performed using SPSS 15.0J for Windows (SPSS, Chicago, IL).

RESULTS — The mean age of the participants was 32.0 years (range 22–40 years) at baseline. The mean ± SD number of fitness tests during 7 years was 6.0 ± 0.96. The time between the first and last fitness test in each single individual was 6.5 ± 0.73 years. The median follow-up time was 14 years, with a total of 56,749 man-years of observation. During follow-up, 274 participants developed type 2 diabetes. There were 42 deaths, and 143 participants were lost to follow-up due to retirement.

Table 1 shows the baseline characteristics of men in each fitness trend quartile. Men in the lowest fitness trend quartile (quartile 1) decreased their average $\dot{V}O_{2max}$ from 45.3 to 36.6 ml/kg/min (median slope −1.25 ml/kg/min) between 1979 and 1985, whereas men in the highest fitness trend quartile (quartile 4) increased their average $\dot{V}O_{2max}$ from 36.3 to 45.6 ml/kg/min (median slope 1.33 ml/kg/min) over the same time. There was an inverse relationship across categories with regard to initial fitness levels. The men in the lowest fitness trend quartile had the highest level of fitness in 1979, whereas those in the highest fitness trend quartile had the lowest level of fitness. The men in the highest quartile were more likely to have lower systolic and diastolic blood pressure and a lower rate of smoking compared with those in the lowest quartile.

Table 2 shows the relationship between potential risk factors and type 2 diabetes risk. Men with higher initial fitness had lower HRs for type 2 diabetes than men in the lower initial fitness group. In addition, older age, high BMI, high systolic blood pressure, alcohol intake, and a family history of diabetes all significantly increased the risk of type 2 diabetes.

Table 3 shows the HRs for type 2 diabetes by fitness trend quartiles, with the lowest quartile used as the referent. There were progressively lower age-adjusted HRs of type 2 diabetes across fitness trend quartiles. After further adjustment for initial fitness level, BMI, systolic blood pressure, cigarette smoking, alcohol intake, and a family history of diabetes, there re-

Table 3—*HRs of incidence of type 2 diabetes, according to quartiles of cardiorespiratory fitness trend*

Variable	Slope (ml/kg/min)	Participants	Man-years of follow-up	No. cases diabetes	Age-adjusted HR (95% CI)	Multivariate HR (95% CI)*
Quartile 1	−1.25 (−6.41 to −0.77)	1,047	14,114	75	1.00 (referent)	1.00 (referent)
Quartile 2	−0.40 (−0.77 to −0.04)	1,048	14,152	82	1.03 (0.75–1.41)	0.64 (0.46–0.89)
Quartile 3	0.32 (0.04–0.73)	1,046	14,212	64	0.77 (0.55–1.07)	0.40 (0.27–0.58)
Quartile 4	1.33 (0.73–6.19)	1,046	14,271	53	0.65 (0.46–0.93)	0.33 (0.21–0.50)
					P_{trend} = 0.005	P_{trend} < 0.001

Data are means (range) unless otherwise indicated. *Adjusted for age, initial cardiorespiratory fitness level, BMI, systolic blood pressure, cigarette smoking, alcohol intake, and a family history of diabetes.

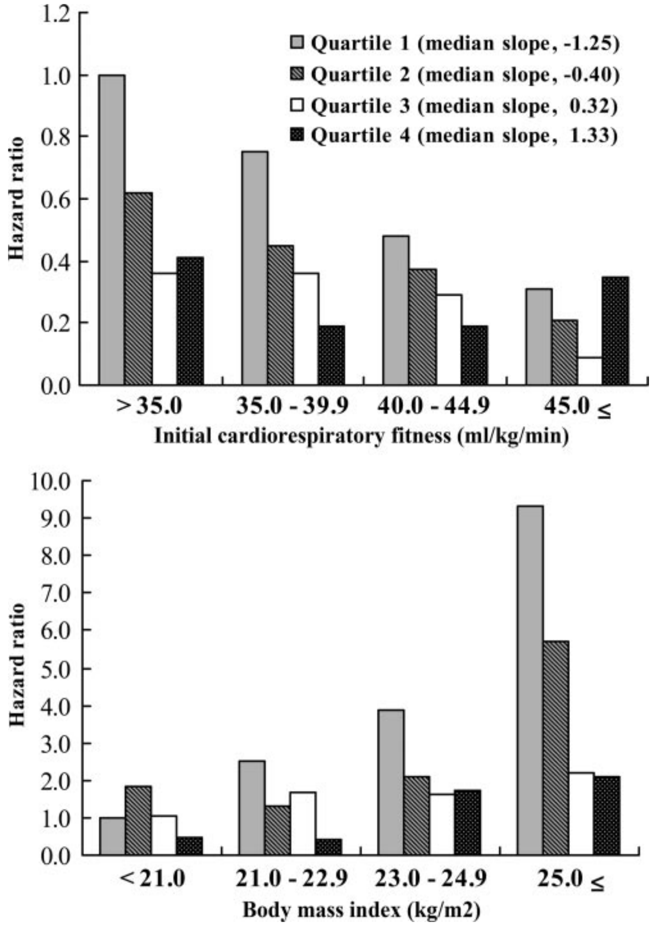

Figure 1—*HRs for incidence of type 2 diabetes associated with quartiles of cardiorespiratory fitness trend, among men categorized by initial (1979) cardiorespiratory fitness level* (top) *or baseline (1985) BMI* (bottom)*. HRs were adjusted for age, systolic blood pressure, cigarette smoking, alcohol intake, a family history of diabetes, and BMI* (top) *or initial cardiorespiratory fitness level* (bottom)*.*

mained a strong inverse association between type 2 diabetes risk and fitness trend quartiles ($P_{trend} < 0.001$). Men in the highest quartile of fitness trend had an ~70% lower risk of developing type 2 diabetes compared with men in the lowest quartile.

We next investigated the HRs of type 2 diabetes associated with quartiles of fitness trend, among men classified according to their initial fitness levels in 1979. (Fig. 1). The inverse gradient for diabetes across long-term trends in fitness categories was generally observed for all levels of fitness in 1979, except for men in the highest category of initial fitness (≥45.0 ml/kg/min). We also investigated the HRs of type 2 diabetes among men with different levels of BMI at baseline (1985). Again, there generally was an inverse gradient for diabetes risk across long-term trends in fitness categories for all BMI categories except the lowest.

CONCLUSIONS — In this study, we prospectively investigated the relationship between long-term trends in fitness and the incidence of type 2 diabetes in nondiabetic Japanese men. There was a strong inverse relationship between long-term trends in fitness and the incidence of type 2 diabetes, with men increasing their fitness over a 7-year period having lower risks than men with decreasing fitness over the same span.

The observed association is biologically plausible, because physical activity or fitness is a strong independent predictor of lower type 2 diabetes incidence rates (2,3). Physical activity or fitness may prevent and delay type 2 diabetes by improving glucose levels, reducing adiposity, increasing muscle mass and the GLUT4 in muscle tissues, and reducing insulin resistance (13,14).

The major strength of this study is the objective measurement of fitness, repeated over time. Fitness, an objective marker of daily physical activity, is a stronger predictor of morbidity or mortality than self-reported physical activity (15). Teräslinna et al. investigated the relationship, among 31 subjects, between measured $\dot{V}O_{2max}$ and estimated $\dot{V}O_{2max}$ using the Åstrand-Ryhming nomogram and correction factors used in the present study, obtaining a correlation coefficient of 0.92 (16). Furthermore, we used values obtained in oral glucose tolerance tests or fasting blood glucose levels as objective measures of the study outcome, type 2 diabetes.

Individuals at high risk of type 2 diabetes, such as those with impaired glucose tolerance or obesity, have been studied in randomized controlled trials of lifestyle, including physical activity and type 2 diabetes (8–10). However, there are no data in low-risk populations. In addition, most of the data have been in Caucasian subjects. Type 2 diabetes is a global problem; thus, data are needed not only in high-risk populations but also in low-risk populations and in other racial/ethnic groups.

One limitation of the present study is that subjects may not be representative of the entire Japanese population and women were not included. Nonetheless, this study provides important and valid information on Japanese male workers. Another limitation is that possible changes in fitness levels were taken into account between 1979 and 1985 but not during the follow-up period, 1985–1999. However, not accounting for changes during the latter period would probably dilute the true association between fitness and the risk of developing diabetes.

In conclusion, this cohort study showed a strong inverse relationship between long-term trends in fitness and the development of type 2 diabetes in Japanese men. This relationship was independent of age, initial fitness level, BMI, systolic blood pressure, cigarette smoking, alcohol intake, and a family history of diabetes. Thus, regular physical activity, which is associated with an increase or preservation of fitness, should be promoted by health professionals, because it decreases the risk of type 2 diabetes, in addition to decreasing the risks of many chronic diseases (17).

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